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EXAMINER
SKELDING, ZACHARY S

ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/687,913	WANK, RUDOLF	
	Examiner	Art Unit	
	Zachary Skelding	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *29-35 and 40-44* is/are pending in the application.

4a) Of the above claim(s) *42* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29-35,40,41,43 and 44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10-20-03 1-12-04*.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *071106* .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment to the claims and election of species, with traverse, filed September 11, 2007 is acknowledged.

Claims 1-28 and 36-39 have been canceled.

Claims 29-35 and 40-44 are pending.

2. Applicant's election of species, with traverse, in the reply filed on September 11, 2007 is acknowledged.

The traversal appears to be on the ground(s) that the species are not independent and/or distinct and that the search of all species can be made without as serious burden. This is not found persuasive for the reasons of record put forth in the Restriction Requirement mailed July 11, 2007, and because applicant has failed to point out with any particularity why the species are not independent and/or distinct or why the search of all species could be made without as serious burden.

Thus, the election of species requirement is still deemed proper and is therefore made FINAL

Applicant has elected the following species:

For the "agent or a single combination of agents that activate T-cells that will be used in the first step" of the method for treating cancer applicant elects "IL2 and anti-CD3";

For the "agent or a single combination of agents that activate T-cells that will be present after the addition of naïve PBMC to the cells stimulated in the first step" of the method of treating cancer applicant elects "IL-2 and anti-CD3";

For the "sources of PBMCs for the first and second PBMC method steps of the invention" applicant elects that the activated antigen presenting cells of the first step and the naïve T cells of the second step are derived from a single cancer patient donor as recited in claim 41.

For the "type of cancer to be treated" applicant elects breast carcinoma.

Thus, claims 29-35 and 40, 41, 43 and 44 are under examination as they read on a method for treating cancer, wherein the elected agent or single combination of agents that activate T cells that will be present in the first and second steps are IL-2 and anti-CD3 antibody; the elected sources of PBMCs for the first and second PBMC method steps of the invention are derived from a single cancer patient donor and the elected type of cancer to be treated is breast carcinoma.

Moreover, claim 42 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

3. Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119 (a)-(d) as shown in the Declaration for Patent Application filed October 20, 2003. A certified copy of the foreign priority application is of record.

However, if applicant desires to claim the benefit of a prior-filed application under 35 U.S.C. 120, a specific reference to the prior-filed application in compliance with 37 CFR 1.78(a) must be included in the first sentence(s) of the specification following the title or in an application data sheet. For benefit claims under 35 U.S.C. 120, 121 or 365(c), the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of the applications.

If the instant application is a utility or plant application filed under 35 U.S.C. 111(a) on or after November 29, 2000, the specific reference must be submitted during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior application. If the application is a utility or plant application which entered the national stage from an international application filed on or after November 29, 2000, after compliance with 35 U.S.C. 371, the specific reference must be submitted during the pendency of the application and within the later of four months from the date on which the national stage commenced under 35 U.S.C. 371(b) or (f) or sixteen months from the filing date of the prior application. See 37 CFR 1.78(a)(2)(ii) and (a)(5)(ii). This time period is not extendable and a failure to submit the reference required by 35 U.S.C. 119(e) and/or 120, where applicable, within this time period is considered a waiver of any benefit of such prior application(s) under 35 U.S.C. 119(e), 120, 121 and 365(c). A benefit claim filed after the required time period may be accepted if it is accompanied by a grantable petition to accept an unintentionally delayed benefit claim under 35 U.S.C. 119(e), 120, 121 and 365(c). The petition must be accompanied by (1) the reference required by 35 U.S.C. 120 or 119(e) and 37 CFR 1.78(a)(2) or (a)(5) to the prior application (unless previously submitted), (2) a surcharge under 37 CFR 1.17(t), and (3) a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The Director may require additional information where there is a question whether the delay was unintentional. The petition should be addressed to: Mail Stop Petition, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

If the reference to the prior application was previously submitted within the time period set forth in 37 CFR 1.78(a), but not in the first sentence(s) of the specification or an application data sheet (ADS) as required by 37 CFR 1.78(a) (e.g., if the reference was submitted in an oath or declaration or the application transmittal letter), and the information concerning the benefit claim was recognized by the Office as shown by its inclusion on the first filing receipt, the petition under 37 CFR 1.78(a) and the surcharge under 37 CFR 1.17(t) are not required. Applicant is still ***required*** to submit the reference in compliance with 37

CFR 1.78(a) by filling an amendment to the first sentence(s) of the specification or an ADS. See MPEP § 201.11.

4. Claim 35 is objected to because it recites "administering CD-3 activated T cells" however the instant specification refers to "CD3-activated T cells." Whatever the nomenclature used it should be consistent throughout the claims and the specification.

5. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o).

Correction of the following is required:

Claim 29 recites, "producing activated antigen presenting cells (APC) by primary stimulation *in vitro* that exposes ***peripheral-blood mononuclear cells (PBMC) obtained from a biopsy*** to anti-CD3 antibodies" and further recites "obtaining naïve PBMC comprising T cells that are ***naïve with respect to one or more cancer antigens***." However, the instant specification does not appear to provide proper antecedent basis for the highlighted phrases shown above.

Moreover, claim 32 and 33 recite "about 30 million" and "about 0.5 cm or less," respectively. Furthermore, claim 40 recites "wherein a cycle of (d') and (d) is repeated up to ten times". However, the instant specification does not appear to provide proper antecedent basis for these limitations.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 29-35 and 40, 41, 43 and 44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 29, and dependent claims thereof, are rejected under 35 U.S.C. 112, 2nd paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01.

In particular, Claim 29, and dependent claims thereof, recites "expanding subsequently in vitro the population of cells (CAPRI cells), derived from the activated naive PBMC...and administering the CAPRI cells into a cancer patient." However, if the skilled artisan is going to specifically "administer the CAPRI cells into a cancer patient" then there must be some step in the claimed method that enables the skilled artisan to distinguish "the population of cells...derived from the activated naive PBMC," i.e., CAPRI cells, from the population of all PBMC cells including those from step (a), since the initial PBMC and the PBMC subsequently added would be otherwise indistinguishable.

Moreover, claim 29, and dependent claims thereof, are further indefinite in their recitation of "obtaining naive PBMC comprising T cells that are naive with respect to one or more cancer antigens." In order for the skilled artisan to "obtain naive PBMC comprising T cells that are naive with respect to one or more cancer antigens" there must be some step in the claimed method that enables the skilled artisan to determine if the PBMC and T-cells they have obtained are indeed "naïve" meaning that they have not yet been activated in vivo by exposure to activating cytokines or antigen presenting cells having a foreign antigen presented on their surface.

Claim 29, and dependent claims thereof, are further indefinite in their recitation of "...administering the CAPRI cells into a cancer patient, wherein the cancer antigens are presented by the activating APC obtained in step (a) to ***the naive T cells*** in the context..." It is unclear if "the naive T cells" refers to the T cells contained within "the naïve PBMC comprising T cells that are naïve with respect to one or more cancer antigens" as recited in step (b) of claim 29 or if it is meant to refer to naive T cells found in the cancer patient to which CAPRI cells have been administered.

Furthermore, claim 41 recites "the method of claim 29, wherein the...PMC activated in step (a)..." However, it is unclear what "the...PMC activated in step (a)..." refers to because step (a) of claim 29 recites to "PBMC" not "PMC".

Applicant is reminded that any amendment must point to a basis in the specification so as not to add new matter. See MPEP 714.02 and 2163.06.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 29-35 and 40, 41, 43 and 44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter Rejection.

In their remarks filed April 16, 2007, at page 8, 1st paragraph, applicant indicates that claim 29 finds support in the claims as originally filed and throughout the specification, for example in claims 1, 14, 23 and 29. However, neither the instant specification nor claims 1, 14, 23 and 29 as originally filed appear to provide written description support for the following claim limitations:

Part (a) of claim 29 recites, "producing activated antigen presenting cells (APC) by primary stimulation *in vitro* that exposes ***peripheral-blood mononuclear cells (PBMC) obtained from a biopsy*** to anti-CD3 antibodies".

While the instant specification provides support for obtaining PBMC from a patient and exposing said PBMC to anti-CD3 antibodies, it does not appear to provide support for exposing "PBMC ***obtained from a biopsy*** to anti-CD3 antibodies."

One of ordinary skill in the art understands that the phrase "PBMC obtained from a biopsy" encompasses in its breadth, for example, PBMC obtained directly from a suspected site of disease, such as a solid B cell lymphoma. However the instant specification does not provide sufficient written description support for exposing "PBMC obtained directly from a suspected site of disease to anti-CD3 antibodies" or therefore for exposing "PBMC obtained from a biopsy to anti-CD3 antibodies".

Claim 29 further recites "obtaining naïve PBMC comprising T cells that are ***naïve with respect to one or more cancer antigens***." However, the instant specification does not provide sufficient support for "obtaining naïve PBMC comprising T cells that are ***naïve with respect to one or more cancer antigens***."

Moreover, claims 32 and 33 as amended August 18, 2006 recite "about 30 million" and "about 0.5 cm or less," respectively. In their Remarks of August 18, 2006 applicant indicates that support for these claims is found on page 12 of the instant specification. However, page 12 of the instant specification does not appear to provide support for these limitations. Indeed, the instant specification appears to explicitly limit the amount of CAPRI cells to be administered to not more than 30 million and intratumor administration when the tumor is no larger than 0.5 cm or less (see, for example, pages 12 and 15, 3rd paragraphs).

Furthermore, claim 40 as amended April 16, 2007 recites "wherein a cycle of (d') and (d) is repeated up to ten times". In their Remarks of April 16, 2007 applicant indicates that support for this claims is found in claims 15-17 as previously presented, which according to applicant's Remarks of August 18, 2006 find support on page 5, lines 3-5 and 15, 30-35 of the instant specification. However, these pages of the specification do not provide support for the claimed limitation. In particular, page 5 is just a generic statement about the invention and page 15 is a discussion of reusing CAPRI cells up to 7 times to destroy a cancer cell line, not about repeating (d) to (d') up to 10 times.

In conclusion, the specification as filed does not provide a sufficient written description of for exposing "PBMC ***obtained from a biopsy*** to anti-CD3 antibodies" or "obtaining naïve PBMC comprising T cells that are ***naïve with respect to one or more cancer antigens***" or for "about 30 million" and "about 0.5 cm or less" or for "wherein a cycle of (d') and (d) is repeated up to ten times". The specification does not provide blazemarks nor direction for these limitations.. These limitations, which do not appear in the specification as-filed, changes the scope of the instant disclosure as-filed. Such limitations introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

Applicant is either required to remove the new matter in the response to this Office action or point out where, in particular, the instant specification provides sufficient written support for the limitations indicated above. See MPEP 714.02 and 2163.06.

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 29-32, 34, 35, 40, 41, 43 and 44 rejected under 35 U.S.C. 103(a) as being unpatentable over Babbitt et al. (5,766,920) in view of Gold et al. (J Surg Res. 1995 Aug;59(2):279-86), Rudolf Wank (WO 99/50393, published in the German language on October 7, 1999, cited by applicant and the English language translation of PCT/EP99/02225, RWS Group plc, September 12, 2000, which is the originally filed application upon which the WO 99/50393 publication is based, cited herewith) and Marzo et al. (J Immunol. 1999 May 15;162(10):5838-45).

Babbitt teaches a method for treating cancer, the method comprising (a) obtaining peripheral-blood mononuclear cells (PBMC) from a cancer patient, (b) exposing said PBMC to anti-CD3 antibodies and IL-2, (c) removing the cell culture supernatant (referred to as "T3CS" by Babbitt) and measuring the levels of IL-2 and anti-CD3 antibodies in the cell culture supernatant, (d) obtaining a second population of peripheral-blood mononuclear cells (PBMC) from the same cancer patient, (e) exposing said second population of PBMC to the T3CS cell culture supernatant including supplemental addition of anti-CD3 antibodies and IL-2 is so desired and (f) administration of the second population of PBMC cells to the cancer patient. (see, in particular, column 2, 1st-3rd paragraphs; column 3, 1st and 4th paragraphs; column 6, 3rd paragraph; column 7, 2nd paragraph; column 18, 1st-3rd paragraphs; column 20, 1st paragraph).

Babbitt further teaches that PBMC polyclonaly-activated independent of tumor-associated antigens according to the invention were cytotoxic to tumor cell lines (see, in particular, paragraph bridging columns 12-13).

However, Babbitt does not explicitly teach that the method for treating cancer can be carried out without the intermediate step of harvesting the cell culture supernatant produced during exposure of the first population of PBMC to anti-CD3 and IL-2 (referred to as "T3CS" cell culture supernatant by Babbitt) and then adding the "T3CS" cell culture supernatant to a second population of PBMC cells obtained from a cancer patient as put forth in the instant claims. Babbitt also does not teach the means of cell administration to the patient including direct injection into a tumor, the dosage range, treatment in conjunction with radiotherapy, administering the second population of PBMCs in conjunction with CD3-activated cells, incubating the second population of PBMCs already exposed to the T3CS cell culture supernatant with a third population of PBMCs obtained from a cancer patient and repeating up to ten times, the use of immobilized anti-CD3 antibodies or particular ratios of first and second populations of PBMCs.

Gold teaches that antigen-specific secondary responses can be recalled ex vivo by anti-CD3 antibody nonspecific activation of PBMC isolated from a cancer patient, even in the absence of specific antigen. Gold further teaches that the major cells activated in this approach are CD44+ memory T-cells, consistent with other reports of memory T-cell activation ex vivo without the requirement for antigen to be present in the culture system. "Therefore, it appears that nonspecific ex vivo activation of lymphocytes from murine and human [tumor-bearing hosts] is capable of generating specific anti-tumor effectors." (see, in particular, paragraph bridging pages 279-280 and page 284, right column, 1st paragraph).

Wank teaches a method for treating brain-associated diseases, the method comprising (a) obtaining peripheral-blood mononuclear cells (PBMC) from a patient, (b) exposing said PBMC to anti-CD3 antibodies, such as immobilized anti-CD3 antibodies, and IL-2, (c) obtaining a second population of peripheral-blood mononuclear cells (PBMC) from the same patient, (d) exposing said second population of PBMC to the first population of anti-CD3 stimulated PBMC and (e) administration of the second population of PBMC cells to the brain-associated disease patient. (see, in particular, page 7, 3rd paragraph to page 8, 1st paragraph; page 21-22, Section 1.2 and page 23, Section 1.4; page 16, 2nd paragraph to page 17, 1st paragraph).

Wank further teaches that upon incubation of PBMC with anti-CD3 antibodies and IL-2, antigen-presenting cells found within the PBMC are stimulated to present "problem proteins or peptides" of the patient so that the immune response can be directed, even in this stage, against said "problem proteins or peptides" (see, in particular, page 14, 2nd paragraph).

In addition, Wank teaches that "one hypothesis to explain the distinctly increased efficiency of 'cascade primed' cells is based on the fact that the cell population resulting from the 'cascade priming' consists, besides specifically enriched activated lymphocytes...in particular of memory T cells." In this same section, Wank further teaches that "[i]t is presumed that "cascade primed" cells are able particularly efficiently to recognize and "treat," i.e., make free of pathogens, cells infected with intracellular organisms." (see, in

particular, page 17, 1st paragraph).

Wank also teaches means of administering and dosing cells to patients as well as ratios of first activated PBMC to second naive PBMC when practicing method of the invention upon which the instant claims read (see, in particular, page 16, 2nd paragraph to page 18, 3rd paragraph and page 23, Section 1.4). Wank further teaches coadministration of CD3-stimulated cells in connection with the administration of "cascade primed" cells to alleviate or avoid the melancholic episode that sometimes follows administration of cascade primed cells ("CAPRI" cells) (See, in particular, page 18, 4th paragraph).

It would have been obvious to one of ordinary skill in the art, and one of ordinary skill in the art would have been motivated to treat cancer by (a) obtaining PBMC from a patient, (b) exposing said PBMC to anti-CD3 antibodies, such as immobilized anti-CD3 antibodies, and IL-2, (c) obtaining a second population of peripheral-blood mononuclear cells (PBMC) from the same patient, (d) exposing said second population of PBMC to the first population of anti-CD3 stimulated PBMC and (e) administration of the second population of PBMC cells to the patient given the reference teachings.

In particular, given the teachings of Babbitt and Gold, it would have been obvious to one of ordinary skill in the art that one can isolate PBMC from a cancer patient, incubate them with anti-CD3 antibodies and IL-2, and without any knowledge of the cancer antigens found in that particular patient, create a second population of activated memory T cells which have tumor specific activity by incubating the cell supernatant collected from the first PBMC incubation (referred to as the "T3CS" cell supernatant by Babbitt) with a second population of naïve PBMC from the same cancer patient.

A difference between the teachings of Babbitt and Gold and the claimed invention is that the method of making autologous activated lymphocytes for treating cancer of Babbitt and Gold involves an intermediate step of harvesting the cell culture supernatant produced during exposure of the first population of PBMC to anti-CD3 and IL-2 (referred to as "T3CS" cell culture supernatant by Babbitt), allowing for quality control analysis and storage of said material before adding it to a second population of PBMC cells obtained from a cancer patient as put forth in the instant claims.

According to Babbitt, "[t]he claimed process employs aliquots of the T3CS generated in advance to be used as a stimulant in the secondary cultures. This approach [ensures that] a full complement of costimulatory signals are available at the initiation of each activation culture and therefore minimizes the probability of generating anergic or apoptotic T cells. Furthermore, use of the pre-manufactured and quality-assured autologous cytokine-OKT3 mixture as a stimulant decreases the dependence upon de novo synthesis of cytokines during the early stage of the subsequent T cell activation cultures. Such decreased dependency is especially important under the conditions such as off-site cell processing that require shipping and storage of the cells and when dealing the with cells from patients of various clinical stages." (see Babbitt, in particular, column 17, 3rd paragraph).

However, given the teachings of Babbitt and Gold, a person ordinary skill in the art applying ordinary creativity, common sense and logic would have immediately appreciated that, while perhaps less amenable to large scale use, it would not be unreasonable to drop the step of generating aliquots of T3CS cell culture supernatant in advance and instead simply (a) obtain PBMC from a patient, (b) expose said PBMC to anti-CD3 antibodies and IL-2, (c) obtain a second population of PBMC from the same patient, (d) expose said second population of PBMC to the first population of anti-CD3 stimulated PBMC, thereby generating cells that can be used for cancer immunotherapy.

Indeed, many of the reasons cited by Babbitt for generating the T3CS cell culture supernatant, "in advance to be used as a stimulant in the secondary cultures" do not prevent one of ordinary skill in the art from practicing the method of treating cancer according to Babbitt but without the step of isolating and storing the T3CS cell culture supernatant by simply devoting more resources to monitoring anti-CD3 and cytokine levels real-time and on-site as the initial population of PBMCs is being exposed to these stimulates, increasing the levels as necessary, and then adding the second population of PBMCs to the first population of PBMCs after sufficient time has passed.

Furthermore, one of ordinary skill in the art would have had a reasonable expectation of success in doing so given the teachings of Wank that it is practical to obtain PBMCs from a patient, albeit a patient with a brain-associated disease, incubate them with anti-CD3 antibodies and IL-2, and without any knowledge of the particular antigens that are provoking said brain-associated disease, such as cells infected with intracellular organisms, create a second population of activated memory T cells which have therapeutic activities in said brain-associated disease patients.

Also, one of ordinary skill in the art would have been motivated to apply the method of making "cascade primed" immunoreactive cells of Wank, to making immunoreactive cells for treating cancer as taught by Babbitt and Gold, because the method of Wank allows for not only generating the cytokine milieu that Babbitt and Gold identify as essential for stimulating the production of activated memory T cells with tumor specific activity, but also for increased cell-based immunostimulation. More particularly, the Wank reference teaches that incubating the first population of PBMC with anti-CD3 and IL-2 induces antigen-presenting cells contained therein to display intracellular peptides (see Wank, in particular, page 12, 1st paragraph to the paragraph bridging pages 12-13 and page 14, last paragraph), and as is well known by one of ordinary skill in the cancer art, extracellular tumor antigens are picked up by antigen-presenting cells and can not only be presented to helper T cells by MHC class II molecules, but also can somehow make their way to MHC class I molecules to "cross-prime" cytotoxic T cells (see, for example, Marzo et al., in particular, Discussion on pages 5842-5845). Thus, one of ordinary skill in the art would have been motivated to apply the method of making "cascade primed" immunoreactive cells of Wank, to making immunoreactive cells for treating cancer as taught by Babbitt and Gold, so as to allow the expansion of tumor specific cytotoxic and T helper cells, both of which are required for effective tumor

eradication (see Marzo, in particular, page 5844, right column).

It is noted that while none of the cited references explicitly teach administration of autologous activated lymphocytes in conjunction with radiotherapy, it would have been prima facie obvious for one of ordinary skill in the art to combine the administration of autologous activated lymphocytes with a conventional cancer therapy, such as radiotherapy, given that radiotherapy has been long known as means of treating cancer and it would have been prima facie obvious to one of ordinary skill in the art to combine these agents in a single method, each of which is taught by prior art to be useful for same purpose, the idea of combining them flowing logically from their having been individually taught in prior art. In re Kerkhoven, 205 USPQ 1069, CCPA 1980. See MPEP 2144.06.

Furthermore, one of ordinary skill in the art would have been motivated to combine the administration of activated PBMC according to the reference teachings with radiotherapy given that it is well known to one of ordinary skill in the art to expect a "synergistic" effect of therapeutic agents when said agents (1) have a common utility, i.e., treating cancer, and (2) have distinct reaction mechanisms, i.e., killing dividing cells with radiant energy and killing cells by immune cell-based mechanisms. Furthermore, one of ordinary skill in the art would have been motivated to do so because, as is well known to one of ordinary skill in the art, synergistic effects often allow for dose reduction of the individual components yielding lower toxicity. Furthermore, one of ordinary skill in the art also readily understands that there are many market pressures to reduce dosing while maintaining treatment efficacy such as reducing the cost of manufacturing.

Given the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in arriving at the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Thus, the instant claims are unpatentable over Babbitt in view of Gold, Wank and Marzo.

12. Claims 29 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Babbitt et al. (5,766,920) in view of Gold et al. (J Surg Res. 1995 Aug;59(2):279-86), Rudolf Wank (WO 99/50393, published in the German language on October 7, 1999, cited by applicant and the English language translation of PCT/EP99/02225, RWS Group plc, September 12, 2000, which is the originally filed application upon which the WO 99/50393 publication is based, cited herewith) and Marzo et al. (J Immunol. 1999 May 15;162(10):5838-45) as applied to claims 29-32, 34, 35, 40, 41, 43 and 44 above, and further in view of Gale Granger (5,837,233) and Johnson et al. (5,217,704).

The teaching of Babbitt, Gold, Wank and Marzo are given in Section 11 above.

The reference teachings of Babbitt, Gold and Wank do not explicitly teach administration of activated PBMCs directly into the tumor of the patient when the tumor is 0.5 cm or less.

However, Granger teaches a method of treating various human tumors comprising incubating PBMCs obtained from the cancer patient with allogenic donor PBMCs ex vivo and then administering the cells directly into the tumor. (see, in particular, columns 10-11 and Examples 1-3). Granger further teaches that cytokine production directly within a tumor can induce tumor regression and that intralesional administration of immunotherapy is considered to be safer than systemic administration (see, in particular columns 1-3).

Moreover, Johnson teaches that "imaging of small, malignant lesions in a human subject in order to treat or cure the malignancy is a prime objective in current cancer treatment. If a malignant lesion or tumor can be detected at a very early stage, treatment through surgery, chemotherapy, radiation or other methods can be performed...the present invention images small malignant lesions with tumor masses from about 0.5 cm in diameter." (see, in particular, column 27, 2nd paragraph).

Thus, it would have been obvious to one of ordinary skill in the art, and one of ordinary skill in the art would have been motivated to treat cancer by administering activated PBMCs generated according to the teachings of Babbitt in view of Gold and Wank directly into a small tumor, such as tumor of 0.5 cm or less. In particular, given that it is easier to treat a small tumor than a larger tumor as is well known by one of ordinary skill in the art and as is echoed by Johnson, and further given that intratumor administration of cells expressing cytokines such as the cells of Babbitt in view of Gold and Wank can induce tumor regression and because of the safety benefits of intratumor versus systemic administration as taught by Granger, one of ordinary skill in the art would have been motivated to treat cancer by administering activated PBMCs generated according to the teachings of Babbitt in view of Gold and Wank directly into a small tumor, such as tumor of 0.5 cm or less.

Given the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in arriving at the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Thus, the instant claims are unpatentable over Babbitt in view of Gold, Wank, Marzo and Granger.

13. No claim is allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary Skelding whose telephone number is 571-272-9033. The examiner can normally be reached on Monday - Friday 8:00 a.m. - 5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Patent Examiner
November 25, 2007

MICHAIL BELYAVSKYI, PH.D.
PRIMARY EXAMINER

11/26/07